REMARKS

Claims 1, 3-15, 17, 31-55, and 57-90 are pending in the present application. By virtue of this response, claims 1, 7, 9, 17, and 62 have been amended and claims 6 and 15 have been cancelled. New claims 91-96 have been added. Accordingly, claims 1, 3-5, 7-14, 17, 31-55, and 57-96 are currently under consideration.

Support for the amendment of claims 1, 9, and 17 can be found in previously pending dependent claims 6 and 15. Support for the amendment can also be found throughout the specification, for example, on page 8, lines 1-10; page 9, lines 20-23; and page 7, lines 25-26 of the specification. Support for new claims 91-93 can be found in the previously pending claims and on page 7, lines 25-26 of the specification. Support for new claims 94-96 can be found in the previously pending claims. No new matter is added.

With respect to claim amendments and cancellation, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Information Disclosure Statement

The Examiner states that the Information Disclosure Statement Applicants submitted on September 7, 2007 has not been considered because the Office Actions cited therein are non-published documents.

Applicants respectfully submit that these Office Actions are cited in the Information Disclosure Statement for the purpose of informing the Examiner about double patenting rejections raised therein against copending, commonly owned patent applications. Specifically, as stated in the September 7, 2007 Information Disclosure Statement, these Office Actions contain rejections of certain pending claims in the corresponding patent applications on the ground of non-statutory

obviousness-type double patenting over claims of the present application. Applicants respectfully request that the Examiner consider and initial the September 7, 2007 Information Disclosure Statement.

Claim Rejections – 35 USC § 112, Second Paragraph

Claims 1, 3-15, 17, 31-55, and 57-90 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

Solely in an effort to expedite prosecution, Applicants have amended independent claims 1 and 9 to recite "wherein the effective amount of the composition is systemically administered in less than about 30 minutes." As discussed above, support for this claim term can be found through out the specification, for example, on page 8, lines 1-10; page 9, lines 20-23; and page 7, lines 25-26 of the specification. Applicants thus respectfully submit that the rejection based on 35 U.S.C. § 112, second paragraph is rendered moot by the claim amendment.

Independent claim 17 already recites "systemically administering to said subject" and is amended to recite "wherein the effective amount of the composition is systemically administered in less than about 30 minutes."

Applicants thus respectfully request that the rejection be withdrawn.

Claim Rejections – 35 USC § 103(a)

Rejections over Desai, Kunz, and Westesen

A. Claims 1, 3-15, 17, 31-33, 38-41, 46-49, 54-55, and 57-90 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Desai et al. (5,439,686) in view of Kunz et al. (5,733,925) in further view of Westesen et at. (6,197,349). Applicants respectfully traverse.

Solely in an effort to expedite prosecution, claims 1, 9, and 17 have been amended to recite "wherein the effective amount of the composition is systemically administered in less than about 30 minutes."

Applicants respectfully submit that, to the extent the Examiner relies on the teaching of drug-coated stent in the cited references, the rejection is obviated by the claim amendment.

Applicants further respectfully submit that the claims as amended are not rendered obvious by Desai in view of Kunz in further view of Westesen.

The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reasons why the claimed invention would have been obvious. MPEP 2141. The Examination Guidelines for Determining Obviousness under 35 U.S.C. § 103 added in MPEP in view of the recent Supreme Court decision *KSR International Co. v. Teleflex*, 127 S. Ct. 1727 (2007), identifies seven rationales that can be used to support the legal conclusion of obviousness. MPEP 2141. One rationale identified in the Examination Guidelines is as follows:

> G. Some Teaching, Suggestion or Motivation in the Prior Art That Would Have Led One of Ordinary Skill To Modify the Prior Art Reference or To Combine Prior Art Reference or To Combine Prior Art Reference Teachings To Arrive at the Claimed Invention.
>
> To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
>
> MPEP 2143.

MPEP further provides that "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP 2143.03.

The Examiner acknowledges that Desai does not teach the claimed methodology of treating non-cancerous cell proliferation in blood vessels. Page 4 of the Office Action.

The Examiner cites Kunz as allegedly disclosing a method of treating non-cancerous cell proliferation in blood vessels, and concludes that it would have been obvious for one of ordinary skill in the art at the time the invention was made to utilize Desai's protein-coated drug for use in the methods disclosed in Kunz. Applicants respectfully disagree.

Kunz provides a number of approaches to treating diseases such as restenosis: (a) targeted therapeutic conjugates containing a vascular smooth muscle cell binding protein coupled to a therapeutic agent dosage form that inhibits a cellular activity of the muscle cell; (b) direct or targeted delivery of therapeutic agents to vascular smooth muscle cells that cause a dilation and fixation of the vascular lumen by inhibiting smooth muscle cell contraction, thereby constituting a biological stent. *See* Abstract. Kunz also describes sustained release dosage forms that are designed to release a therapeutic agent therefrom for a time period ranging from about 3 to about 21 days. *See e.g.*, column 3, line 63 to column 4, line 34; column 10, lines 7-11. These sustained release dosage forms can be in the form of microparticles or nanoparticles. Column 4, lines 22-34; column 14, line 34 to column 17, line 11.

Kunz does not teach or suggest methods claimed in the present application, or provide a motivation to combine with Desai to arrive at methods claimed in the present application. Specifically, Kunz, alone or in combination with Desai, does not teach or suggest methods of treating hyperplasia of non-cancerous cells in a blood vessel (or inhibiting cell proliferation) comprising administering to a subject an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a coating consisting essentially of protein, wherein the effective amount of the composition is systemically administered in less than about 30 minutes.[1]

[1] The Examiner had suggested the claimed language "consisting essentially of" during the interview of September 26, 2006 when discussing Kunz.

In fact, Kunz would have led a person of ordinary skill in the art away from the claimed invention. For example, Example 5 of Kunz provides a study of the effect of a targeted therapeutic conjugate, namely, a conjugate of the targeting protein NR-AN-01 and the therapeutic agent Roridin (RA), on cellular activities (such as protein synthesis) by exposing the conjugate to cultured cells for 5 minutes. It was disclosed that the targeted therapeutic conjugate, but not the free therapeutic agent, showed a short-term specific reversible effect on target cells. Consistent with this result, it was disclosed that the targeted therapeutic conjugate, but not the free therapeutic agent, was effective in inhibiting cell proliferation when administered intraarterially for 45 seconds to 3 minutes into a traumatized vessel in a pig model. Examples 6-7. A person of ordinary skill in the art reading Kunz would have been led to understand that short term administration of a composition lacking a targeting protein would have been ineffective in inhibiting cell proliferation.

Similarly, given the fact that therapeutic agents not conjugated to a targeting protein were ineffective in inhibiting cell proliferation under the testing conditions of Examples 5-7, a person of ordinary skill in the art would not have reasonably expected that systemic administration of a composition that is not conjugated to a targeting moiety (such as compositions recited in the present claims) in less than about 30 minutes would lead to inhibition of cell proliferation and treatment of hyperplasia.

The Examiner refers to various places in Kunz which relate to the various approaches of Kunz, none of which teaches or suggests the claimed methods. The Examiner refers to Examples 3, 5, and 14 of Kunz as allegedly teaching administration of a therapeutic agent in less than three to five minutes. Example 5 is discussed above. Example 3 states,

> For administration by i.v. catheter, it is desirable that the therapeutic conjugate of the invention be administered in less than 3 to 5 minutes, so that blood flow can be reestablished in the patient. Therefore, studies were conducted to determine the binding kinetics of a smooth muscle binding protein with a Ka of $>10^9$ liter/mole.
>
> Column 46, lines 18-22.

After making a general statement regarding desirability of delivery time for a certain mode of delivery of the therapeutic conjugate, Example 3 goes on to discuss the *in vitro* experiment and

concludes that the targeting protein (NR-AN-01) binds to target cells within 5 minutes at low dose levels. Thus, Example 3 focuses specifically on the delivery of the targeted therapeutic conjugate.

Example 14 evaluates use of cytochalasin B as a "biological stent," a process involving inhibition of smooth muscle cell contraction, not inhibition of cell proliferation. Kunz provides no motivation for a person of ordinary skill in the art to use the administration method disclosed in Example 14 of Kunz, which is designed to achieve the biological stenting effect, for a method of inhibiting cell proliferation or treating hyperplasia. A person of ordinary skill in the art reading Kunz would not have had a reasonable expectation that inhibition of cell proliferation and treatment of hyperplasia can be achieved by following the same administration method disclosed in Example 14 of Kunz.

Westesen does not cure the deficiencies discussed above. Westesen is cited as allegedly teaching use of an amorphous form of a poorly water-soluble drug to provide better solubility and bioavailability of the poorly water-soluble drug than utilizing a crystalline form. Westesen does not disclose method of treating non-cancerous cell proliferation in blood vessels, or systemically administering an effective amount of a nanoparticle drug composition in less than about 30 minutes for such purpose.

Applicants thus respectfully submit that Desai, Kunz, and Westesen, alone or in combination, do not render the claims obvious. Applicants respectfully request that the rejection be withdrawn.

B. Claims 34, 35, 42, 43, and 50-51 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Desai et al. (5,439,686) in view of Kunz et al. (5,733,925) in view of Westesen et al. (6,197,349) in further view of Hunter (5,994,341). Applicants respectfully traverse.

As discussed above, claims 1, 9, and 17 have been amended to recite "wherein the effective amount of the composition is systemically administered in less than about 30 minutes." As further discussed above, Desai, Kunz, and Westesen, alone or in combination, do not render claims of the present application obvious.

Hunter (5,994,341) is cited as allegedly teaching that both epothilone and paclitaxel disrupt microtubule function. Hunter (5,994,341) does not cure the deficiencies discussed above. Accordingly, Applicants respectfully submit that the cited references do not render claims of the present application obvious. Applicants respectfully request that the rejection be withdrawn.

C. Claims 36-37, 44-45, and 52-53 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Desai et al. (5,439,686) in view of Kunz et al. (5,733,925) in view of Westesen et al. (6,197,349) in further view of Gregory (Transplantation, vol. 59, pp. 655-661, 1995). Applicants respectfully traverse.

As discussed above, claims 1, 9, and 17 have been amended to recite "wherein the effective amount of the composition is systemically administered in less than about 30 minutes." As further discussed above, Desai, Kunz, and Westesen, alone or in combination, do not render claims of the present application obvious. Gregory is cited as allegedly teaching that rapamycin is an immunosuppressant which has an antiproliferative action that is useful in the treatment of arterial thickening after injury such as angioplasty. Gregory does not cure the deficiencies discussed above. Accordingly, Applicants respectfully submit that the cited references do not render claims of the present application obvious. Applicants respectfully request that the rejection be withdrawn.

Rejections over Hunter, Yapel, Kunz, and Westesen

A. Claims 1, 3-15, 17, 31-33, 34-35, 38-41, 42-43, 46-49, 50-51, 54-55, and 57-90 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hunter et al. (5,716,981) by itself or in view of Yapel (4,147,767) in further in view of Kunz et al. (5,733,925) and Westesen et al. (6,197,349).

As discussed above, claims 1, 9, and 17 have been amended to recite "wherein the effective amount of the composition is systemically administered in less than about 30 minutes." Applicants respectfully submit that Hunter et al. (5,716,981), Yapel, Kunz, and Westesen, either alone or in combination, do not render claims of the present application obvious.

The Examiner alleges that Hunter et al. (5,716,981) implicitly teaches the claimed administration by teaching insertion of a drug coated stent. As discussed above, the claims have been amended to recite "wherein the effective amount of the composition is systemically administered in less than about 30 minutes," which clearly do not encompass deployment of a stent.

The Examiner alternatively relies on Kunz for teaching of the claimed administration time. However, as discussed above, Kunz does not teach or suggest methods comprising administering to a subject an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a coating consisting essentially of protein, wherein the effective amount of the composition is systemically administered in less than about 30 minutes. Furthermore, as discussed above, Kunz teaches away from such a method.

Yapel does not cure the deficiency discussed above. Specifically, Yapel is cited as allegedly teaching use of albumin as a medicament carrier for intravascular injection. Yapel does not disclose method of treating non-cancerous cell proliferation in blood vessels, or systemically administering an effective amount of a nanoparticle drug composition in less than about 30 minutes for such purpose.

Applicants thus respectfully request that the rejection be withdrawn.

B. Claims 36-37, 44-45, and 52-53 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hunter et al. (5,716,981) by itself or in view of Yapel (4,147,767) in view of Kunz et al. (5,733,925) and Westesen et al. (6,197,349) in further in view of Marx (Circ. Res. Vol. 76, pp. 412-417, 1995). Applicants respectfully traverse.

As discussed above, Hunter et al. (5,716,981), Yapel, Kunz and Westesen, alone or in combination, do not render claims of the present application obvious. Marx is cited as allegedly teaching rapamycin as an inhibitor of smooth muscle cells in the abnormal proliferation of restenosis. Marx does not cure the deficiencies discussed above. Accordingly, Applicants respectfully submit that the cited references do not render claims of the present application obvious and request that the rejection be withdrawn.

Double Patenting

Claims 1, 3-41, 46-49, and 52-90 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims in three copending applications. Specifically, claims 1, 3-17, 31-32, 38-40, 46-48, and 54-90 are rejected over claims 1-2, 5-13, 16-17, 21, and 24 of copending application No. 11/544,242; claims 1, 3-17, 31-32, 38-40, 46-48, and 54-90 are rejected over claims 1-2 and 5-18 of copending application No. 11/594,417; and claims 1, 3-15, 17, 31-33, 36-41, 46-49, 52-53, 54-55, and 57-90 are rejected over claims 1-49 of copending application No. 11/359,286, respectively, in view of Kunz.

Applicants respectfully request that these provisional projections be held in abeyance until the Office has made a determination of otherwise allowable claims in the present application or in copending Application Nos. 11/544,242, 11/594,417, 11/359,286.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 638772000127. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: May 9, 2008

Respectfully submitted,

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